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A Model to Evaluate Past Exposure to 2,3,7,8-TCDD

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ABSTRACT

Data from several studies suggest that concentrations of dioxins rose in the environment from the 1930s to about the 1960s/70s and have been declining over the last decade or two. The most direct evidence of this trend comes from lake core sediments, which can be used to estimate past atmospheric depositions of dioxins. The primary source of human exposure to dioxins is through the food supply. The pathway relating atmospheric depositions to concentrations in food is quite complex, and accordingly, it is not known to what extent the trend in human exposure mirrors the trend in atmospheric depositions.

This paper describes an attempt to statistically reconstruct the pattern of past human exposure to the most toxic dioxin congener, 2,3,7,8-TCDD (abbreviated TCDD), through use of a simple pharmacokinetic (PK) model which included a time-varying TCDD exposure dose. This PK model was fit to TCDD body burden data (i.e., TCDD concentrations in lipid) from five U.S. studies dating from 1972 to 1987 and covering a wide age range. A Bayesian statistical approach was used to fit TCDD exposure; model parameters other than exposure were all previously known or estimated from other data sources.

The primary results of the analysis are as follows: 1.) use of a time-varying exposure dose provided a far better fit to the TCDD body burden data than did using a dose that was constant over time; this is strong evidence that exposure to TCDD has, in fact, varied during the 20th century, 2.) the year of peak TCDD exposure was estimated to be in the late 1960s, which coincides with peaks found in sediment core studies, 3) modeled average exposure doses during these peak years was estimated at 1.4 to 1.9 pg TCDD/kg-day, and 4) modeled exposure doses of TCDD for the late 1980s of less than 0.10 pg TCDD/kg-day correlated well with recent estimates of exposure doses around 0.17 pg TCDD/kg-day (recent estimates are based on food concentrations combined with food ingestion rates; food is thought to explain over 90% of total dioxin exposure). This paper describes these and other results, the goodness-of-fit between predicted and observed lipid TCDD concentrations, the modeled impact of breast feeding on lipid concentrations in young individuals, and sensitivity and uncertainty analyses.

INTRODUCTION

Data from various sources suggest that concentrations of dioxins in the environment have been decreasing over the last decade or two. The most direct evidence of this trend comes from lake core sediments, which show a rise in concentrations of dioxins starting from about the 1930s up until the 1960s or 1970s, and a decline thereafter through about the mid 1980s, which is as far as the sediment core data go (Kjeller and Rappe, 1995; Alcock and Jones, 1996; Beurskens et al.; 1993; Cleverly et al., 1996; Czuczwa et al., 1985a; Czuczwa, et al., 1985b). Other data, particularly from Europe, suggest declines in vegetation, fish, food products, and even human breast milk in the 1980s and into the 1990s (Kjeller, et al., 1991; Furst and Wilmers, 1995; MAFF, 1995; Huestis et al., 1997). There is also limited evidence of declines in blood serum levels in the United States during the 1980s (EPA, 1991).

Human exposure to dioxins is thought to come primarily from animal products such as meat, dairy products and fish. Other routes of exposure, such as inhalation, water ingestion, or soil related exposures are expected to be minimal (< 5%) for the dioxins (EPA, 1994 and others). Average dioxin concentrations in various food products have been estimated and combined with average food ingestion rates to provide current estimates of dioxin exposure. Based on data from the late 1980s and early 1990s, EPA (1994) recently estimated exposures of 1.7 pg dioxin toxic equivalents (TEQ)/kg-day and 0.17 pg 2,3,7,8-TCDD/kg-day. However, since there is very limited data on dioxin concentrations in food before the late 1980's, it is not possible to directly estimate past human dioxin doses in the same manner. Have average dioxin doses been declining and do trends over time in human dioxin body lipid concentrations mirror those found for lake sediments and other sources?

This paper attempts to indirectly reconstruct the background human dioxin dose history by combining recent data on human tissue concentrations of the most toxic dioxin congener, 2,3,7,8-TCDD (abbreviated TCDD hereafter), in individuals in the United States with a first-order, single compartment pharmacokinetic (PK) model which relates exposure history to tissue concentrations. Although tissue concentration data go back only to the early 1970's, the long half-life of TCDD in the body (on the order of 10 years) implies that current concentrations are influenced by exposures decades in the past. The basic idea used here is to take a parameterized function $e(t,\theta)$ of exposure through time, substitute it into a PK model for TCDD, and determine how closely different θ predict the pattern of TCDD concentrations by age and year seen in several studies. Because, as described above, there is some indirect knowledge about past TCDD exposure, and because many possible curves of exposure through time could lead to optimal fits of the human age-by-year concentration data, a Bayesian approach to estimating exposure parameters was utilized.

The approach here builds conceptually on the work of Van Der Molen et al. (1996) who used a PK model and a parameterization of past exposure to try to fit TCDD concentrations reported in a German population in 1991. Unlike our analysis, Van Der Molen et al. (1996) did not employ a Bayesian approach and did not try to fit multiple data sets. Our analysis also utilizes a different PK model and a different exposure parameterization than were reported in Van Der Molen et al. (1996).

STATISTICAL AND MATHEMATICAL METHODS

Section A describes the human TCDD concentration data used here to make inferences about past exposure; all of these data are from subjects with no known direct exposure to dioxin. Then, in Section B, we describe the PK model for TCDD and its parameterization, including derivation of population physiologic parameters, and show how it can be used to predict mean concentrations by age, sex and specimen year. In Section C, the parameterization of the average exposure function $e(t,\theta)$ and the details of the Bayesian analysis are discussed, including the construction of the prior distribution on θ. Finally, in D, aspects of assessing model fit are discussed.

A. Sources of Data

Table 1 gives a summary of the human lipid concentration data. Andrews et al. (1989) studied surgical patients in Missouri considered not to be directly exposed to dioxin; the means displayed in the table are the published age group means. For the Air Force study reported in Michalek et al. (1997; abbreviated AF), the raw data on TCDD levels in the blood lipid of control group subjects were obtained and the mean concentrations for 5 year age groups were calculated. These controls were veterans not thought to have had direct contact with Agent Orange, unlike the exposed, or "Ranch Hand", subjects in the study. The National Human Adipose Tissue Surveys (NHATS) (EPA, 1991) are nation-wide surveys of lipids from surgical patients and cadavers. The 1982 and 1987 NHATS (NHATS 82, NHATS 87) utilized composite samples to measure TCDD levels; we utilize here the mean age group concentrations as estimated by Orban et al. (1994) using a linear additive model. The VA/EPA study (VA/EPA, 1988; Stanley et al., 1990) analyzed stored non-composite samples from NHATS dating from 1970 to 1982; the values in Table 1 are the reported mean tissue TCDD concentrations.

The last column of the table gives estimates for the standard errors (SEM's) of the reported age/year group means. For each of the studies using non-composited samples (Andrews et al., (1989), AF, and VA/EPA), the variance of individual concentrations was assumed constant over all age/year groups and was estimated by the pooled variance across groups; the SEM's were then computed as the square root of the pooled variance estimate divided by the number of subjects in the group. For the composited studies (NHATS 82 & 87), where a linear model was used to generate the age group means, the SEM's given in Table 1 are the corresponding standard errors of these means based on the model.

B. TCDD PK Model

A first order, one-compartment PK model was used to compute an individuals' TCDD concentration in lipid through time. Specifically, the model takes the form:

$$da(t)/dt = f\ D(t) - k(t)\ a(t) \qquad (1)$$

$$c(t) = \frac{a(t)}{1000\ V(t)} \qquad (2)$$

where:

a(t)	=	amount of TCDD in lipid (pg) at time t
c(t)	=	concentration of TCDD in lipid (pg/g) a time t
D(t)	=	exposure dose of TCDD (pg/yr) at time t
V(t)	=	lipid weight (kg) at time t
k(t)	=	elimination rate (yrs^{-1}) at time t
t	=	time (yrs)
f	=	fraction of dose absorbed into lipid compartment (unitless)

Two recent studies, Michalek et al. (1996) and Flesch-Janys et al. (1996), estimated k in the framework of the above model by using paired specimens from individuals with high TCDD concentrations. Both showed that k was a function of percent body fat, and Flesch-Janys et al. (1996) showed that it was also a function of age. In both studies, percent body fat was estimated from a subject's weight and height (and sex) based on a formula which did not take into account the subject's age. The formula used in both studies, developed by Knapik et al. (1983), was based on data from military recruits predominantly 18-25 years of age; this formula was shown to be a good predictor of body fat in this age group. However, numerous studies have shown that formulas based on body mass index (BMI), or weight and height, that do not take age into account, are biased and may underestimate percent body fat in older persons (Deurenberg et al., 1991; Roubenoff et al., 1995). Because reconstruction of exposure history is sensitive to age-related changes in the PK model, we re-performed the Michalek et al. (1996) analysis using a different algorithm for calculating percent body fat from BMI. Specifically, we used the algorithm developed by Deurenberg et al. (1991), who conducted separate regressions for children (under 16) and adults to derive expressions for percent body fat as a function of BMI, age and sex. 'True' percent body fat in the Deurenburg study was calculated by using underwater weighing to estimate body density and then using the Siri formula (which calculates percent body fat from body density).

We obtained the raw data used in Michalek et al. (1996), calculated percent body fat based on the Deurenberg formulas, and re-performed the same statistical analysis as in Michalek et al. (1996). As in Michalek et al. (1996), the elimination rate k was modeled as follows:

$$k(t) = k_0 + k_1 (F(t) - 25) \qquad (3)$$

where:

k_0	=	elimination rate at 25% body fat (yrs^{-1})
k_1	=	change in elimination rate with % body fat (yrs^{-1})
F(t)	=	% body fat at time t = 100*V(t)/W(t)
W(t)	=	total body weight (kgs) at time t

Our analysis yielded estimates of 0.0775 for k_0 and -.00313 for k_1 ; for comparison, the estimates reported in Michalek et al. (1996) were 0.0665 for k_0 and -0.00314 for k_1 .

The other unknown parameter from Equation (1) is the absorption fraction, f. Fries and Marrow (1975) found that 50-60% of the TCDD in feed was absorbed by rats. Rose, et al. (1976) estimated that 86% of the TCDD in a mixture of acetone and corn oil fed by gavage to rats was absorbed, while Dilberto et al. (1996) estimated 88% TCDD absorption for oral-gavage treated rats. From these and similar studies, it will be assumed that f is equal to 0.8.

Since the primary route of exposure to dioxin is ingestion, it was assumed that the exposure dose D, which represents the amount taken into the body, is proportional to body weight:

$$D(t) = 365\ e(t)\ W(t) \qquad (4)$$

where:

D(t) = annual exposure dose of TCDD (pg/yr)
e(t) = daily exposure dose of TCDD per kilogram body weight (pg/kg-day)

The dose of dioxins through consumption of breast milk may be significantly higher than background. EPA (1994) estimated that the dose to breast-fed infants was about 60 pg of TEQ/kg-day, compared to a background dose estimated by EPA (1994) of 1.7 pg TEQ/kg-day. This can result in higher body burdens of dioxins in breast fed versus non breast fed infants and children. Abraham et al. (1995) studied dioxin levels in a breast and a formula-fed infant at 11 and 25 months of age and found that, at both ages, the body burden of dioxin-like compounds was more than an order of magnitude higher in the breast-fed infant.

Based on this trend, we included a breast-feeding component to the exposure dose e(t). We followed the approach of Smith (1987) in assuming an equivalence between dioxin concentrations in breast milk lipid and in the mother's lipid compartment. Based on data in EPA's *Exposure Factors Handbook* (1996), we assumed a daily intake of 26 g of breast milk lipid, an average breast-feeding duration of 4 months and a mother's age of 25 years. The incorporation of breast milk exposure into the concentration estimates is described further below.

For any past exposure function e(t), the above PK model was used to generate expected mean concentrations of TCDD in body lipids in the age/year groups displayed in Table 1. These expected mean concentrations are denoted as E(Y_i|e(t)) for the ith group in the table. To do this, it was first necessary to specify weight and lipid volume as functions of age for an "average" male and an "average" female. We denote these functions W_f,W_m, and V_f,V_m. Data from the National Health and Nutrition Survey (NHANES) on mean weight by age and sex were used to generate W_f and W_m (Hamill et al., 1977; Abraham et al., 1979). V_f and V_m were generated by multiplying weight by the average proportion body fat F_f or F_m, where the latter were generated by taking the mean BMI by age and sex from NHANES and substituting them into the Deurenberg et al (1991) formulas described above. With these functions set, the expected mean concentration in an age/year group was computed as follows:

1. A range of birth years for persons in the group was determined based on the age range and specimen year (for the EPA/VA study where a 3-year range is given, the midpoint is used for specimen year).
2. For each birth year, the model described in Equations (1,2) was solved numerically for

the lipid concentration in the specimen year for breast-fed males, breast-fed females, non-breast-fed males and non-breast-fed females. For the breast-fed cohorts, exposure e(t) for the first four months of life was determined by multiplying average breast milk lipid intake (26 g) by the average TCDD concentration in females born 25 years prior.

3. Concentrations for all birth years in the group were averaged to give predicted group mean concentrations by sex and breast feeding status. It was determined that the effect of breast feeding would only be seen in the two under-15-years age groups (NHATS 82 and 87) which represent births from 1968 to 1987. Based on data from EPA's *Exposure Factors Handbook* (EPA, 1996), a 50% breast feeding rate was assumed for this time period. The predicted means for each group in Table 1 were thus determined by taking the appropriate averages of the sex by breast-feeding group means (i.e., males and females were averaged if the group contained both sexes and breast-fed and non breast fed were averaged for the two under 15 year age groups) .

We assume that the mean concentrations in a group are normally distributed with variance equal to the square of the SEM's listed in Table 1. Then, suppressing the constant term, it follows that the probability density for the group mean data Y given an exposure function e(t) is:

$$Prob(Y|\ e(t)) \quad = \quad \Pi_i \ \exp \frac{-.5 * [Y_i \ - \ E(Y_i|e(t))]^2}{SEM_i^2} \qquad (5)$$

C. Parameterization of Exposure and Construction of Prior Distribution

As discussed in the introduction, we felt that a Bayesian approach would be most useful here in attempting to make inferences about past exposure. As a first step, knowledge of the environmental dioxin trends discussed in the introduction, including data from lake sediment cores, herbage, and other sources, was used to help suggest the general form of a parameterized exposure function e(t,θ). This function was thought to have a single peak somewhere in the mid to late 20th century and to generally be rather smooth. Another concern was that the dimension of θ be high enough to allow for a wide variety of possible shapes but not so high that searches of the parameter space would be intractable. Finally, we wanted e(t,θ) to also depend on an auxiliary parameter r for which various values could be pre-specified so that the effect of different parameterizations could be studied. These considerations suggested the following functional form for the exposure function e(t,θ) = e(t,θ,r):

$$e(t,\theta,r) \quad = \quad b \ + \ e^{h \ - \ sb \ (u \ - \ t)^r} \qquad t \ < \ u \qquad (6a)$$

$$e(t,\theta,r) \quad = \quad b \ + \ e^{h \ - \ sf \ (t \ - \ u)^r} \qquad t \ \geq \ u \qquad (6b)$$

where:

θ	=	(u,b,h,sb,sf)
u	=	time of peak exposure (years)
b	=	baseline exposure dose (pg/kg-day)
h	=	log of peak exposure above baseline (log [pg/kg-day])
sb (>0)	=	rate of decline in log exposure above baseline backward in time from peak year (log [pg/kg-day] yr^{-r})
sf (>0)	=	rate of decline in log exposure above baseline forward in time from peak year (log [pg/kg-day] yr^{-r})
r	=	auxiliary steepness parameter (unitless) ; pre-set at 0.5, 1, 2

The next step was to develop a prior distribution $\Pi(\theta)$ on θ. Our approach was to use environmental trend data on TCDD to create a subset X of the θ parameter space for which the exposure curves were thought to be plausible, and then have the prior be uniform in X. The plausibility criteria are based on five time trend studies of TCDD (summarized in Table 2) and one current estimate of exposure dose of TCDD. These data suggest the following trends: 1) a peak in sediment cores and herbage samples occurred in the 1960s or 1970s, 2) early century levels are from 2 to >33 times lower than the peak, 3) late 1980s levels are from 1 to 20 times lower than the peak, and 4) a trend that late 1980s levels are higher than early century levels; in all cases, the ratio of peak to 1980s levels is lower than the ratio of peak to early century levels. The current estimate of exposure dose (EPA, 1994), based on food concentrations and average consumption rates, was 0.17 pg TCDD/kg-day; this estimate was for circa 1990. Assuming that 90% of exposure is from food sources, we find an estimate of exposure of 0.19 pg/kg-day.

Based on these trends, the following criteria were established for plausibility:

1. A range of 0.0 to 0.50 pg/kg-day for the exposure dose in 1990. We used the same plausible range for the 1900 dose.
2. Ranges of 2-200 for the ratio of peak to 1900 dose and 1-100 for peak to 1990 dose.
3. Peak year was set between 1945 and 1980.

Finally, we set limits on the rate of decrease from the peak exposure level going forward or backward one year in time; this limit was set at 20%. This criteria was established to insure a smooth exposure curve. It was relatively straightforward to translate these plausibility criteria into a subset X of parameter space for which $\Pi(\theta)$ was uniform.

Clearly, there is some arbitrariness in these ranges, and the soundness of assuming uniform distributions could be questioned. These concerns are partially addressed by a sensitivity analysis on the prior, the results of which are discussed in the next section.

Following Bayes theorem, the a-posteriori distribution θ is given by:

$$Prob\ (\theta|Y) \quad = \quad \frac{Prob\ (\theta,Y)}{Prob\ (Y)} \tag{7a}$$

$$= \quad \frac{Prob\ (Y|\theta)\ \Pi\ (\theta)}{\int Prob\ (Y|\theta)\ \Pi\ (\theta)} \tag{7b}$$

This distribution was used to generate expected values and (equal tail) credible sets for various functions of the exposure curve e(t,θ,r). Recall that a p% equal tail credible set for a function g(θ) is an interval [a,b] such that a and b are equal to the (100p/2)th and the 100(1-p/2)th percentiles, respectively, of the distribution of g(θ) (Carlin and Louis, 1996); this latter distribution, of course, is derived from Prob(θ|Y). We calculated expected values and credible sets for the following functions of past exposure: year of peak exposure; average exposure dose over the 10 year interval with highest average exposure, denoted e(peak10); the average dose for the period 1910-1940, denoted e(10-39); and the average dose for each of the decades from the 1940s to the 1980s, denoted e(40s), e(50s), etc. Note that probability statements about credible sets, e.g., that the probability that g(θ) falls in the credible set is p%, apply to each function individually, not jointly to all the functions.

D. Assessing Goodness of Fit

The above exposure models, e(t,θ,r), were used for making inferences about past exposure. However, to help assess the goodness of fit of these models, we also considered two alternate exposure models, or parameterizations, e(t,ϕ) and e(t,CONST). The first, e(t,ϕ), was a very high dimensional parameterization with virtually no plausibility conditions. The idea behind it was that it represents a lower bound on how well the group mean data can be reproduced using the PK model and parameters employed here, even if our e(t) curve truly represented average exposure. For e(t,ϕ), distinct parameters represented the average exposure dose for the following: 1) each five year interval from 1910 to 1945, 2) each three year interval from 1946 to 1962, and 3) each year from 1963 to 1987 (38 parameters in all). The only constraints were that e(t) be less than 50 pg/kg-day. The other parameterization, e (t,CONST), was simply the constant exposure model. For both e(t,ϕ) and e(t,CONST), no prior distribution was assumed; we simply searched for a parameter that minimized the likelihood Prob(Y|e(t)).

In both the Bayesian and non-Bayesian contexts, the AIC (Akaike's Information Criterion) can be used to compare goodness of fit across exposure models (Carlin and Louis, 1996); here AIC is given by the minimum over the parameter space of [-2 log Prob(Y|e(t)) + 2(# params)]. To assess whether a specific exposure curve is compatible with the (human concentration) data, note that if e(t) were the true mean exposure curve, then -2 log Prob(Y|e(t)) =CHI_{GOF} would be

distributed as a chi-square random variable with 22 (the number of groups) degrees of freedom. The probability of a chi-square random variable (with 22 d.f.) exceeding CHI_{GOF} can be taken as the "p-value" of the specific e(t), i.e., the probability, given that the e(t) is the true exposure curve, of observing results more extreme than those currently observed.

RESULTS

A. Goodness of Fit

Table 3 displays AIC results for the various exposure models e(t,...). The models e(t,θ,r) with r=1 and r=2 had roughly similar AIC's and both were considerably better than the e(t,θ,.5) model or the constant exposure model, e(t, CONST). Table 3 also displays CHI_{GOF} values for the best fitting e(t,.) for each model. It is seen that these values considerably exceed the 99th percentile of the appropriate chi-square distribution. By this criterion, then, none of the models adequately fit the observed group means. Table 4 displays observed versus predicted means by age/year group; predicted means were generated using the best fitting exposure curves for the e(t,θ,r) model with r=1 and r=2. Also shown are the corresponding z-scores, i.e., the predicted minus the observed mean divided by the standard error of the mean.

Comparing the NHATS 82 and 87 data, we see that the mean increases considerably (from 1982 to 1987) in the oldest age group (45+) but decreases considerably in the two younger age groups. Further, the NHATS 82 data do not display the trend of increasing TCDD concentrations by age seen in most other studies done in the 1980's (mean was 6.9 pg/g in the 15-44 group and 5.5 pg/g in 45+ group) while the age trend in NHATS 87 (mean of 4.4 pg/g in the 15-44 age group versus 9.4 pg/g in the 45+ age group) seems exaggerated. These trends are hard to explain with the current modeling structure, and subsequently, all good fitting models over-predicted the 1982 mean and under-predicted the 1987 mean in the highest age group. This apparent inconsistency in the human data partially explains why even the high dimensional parameterization of exposure, e(t,ϕ), gave a CHI_{GOF} value (107) that also considerably exceeded the critical chi-square value of 40.3; in fact, this 38 parameter model did not decrease CHI_{GOF} that much over the five parameter r=1 and r=2 models. Note that the above CHI_{GOF} value of 107 for the e(t,ϕ) model represents a lower bound on the best possible fit of any plausible exposure curve because it was generated from an e(t,ϕ) curve that was not plausible.

It is also of interest to see whether possible mis-specification of the PK parameters could help explain the lack of fit of even the high dimensional exposure model. To test this, we allowed k_0 and k_1 to vary within their 95% confidence intervals when fitting the e(t,ϕ) model; this only improved CHI_{GOF} from 107 to 85.

Notwithstanding then the fact that the e(t,θ,r) model (with r=1 or r=2) does not adequately fit the group mean data, we believe the above considerations show that the resultant exposure estimates derived from these models are still useful. These models fit the data much better than does the constant exposure model. Further, the lack of fit is not primarily due to a lack of flexibility in the exposure parameterization. Also, we do assess changes in exposure characteristics due to changes in the PK parameters, in Section D below.

B. Characteristics of Exposure

Because the r=0.5 model fits so much worse than the r=1 or r=2 model, we do not

consider this model further and concentrate on the exposure results of the r=1 and r=2 models. Figure 1A,B displays some exposure curves e(t,θ,r) corresponding to the most likely (a-posteriori) values of θ. For both r=1 and r=2 there is marked divergence in these curves even as the associated likelihoods (i.e., Prob(Y|θ)) are quite similar; this clearly indicates the existence of multiple local maxima of the likelihood function. As would be expected, this divergence increases as one goes further back in time. For r=1 (Figure 1A), these curves differ greatly until about the late 1960's, after which point they are all quite similar. A similar trend is seen for r=2 (Figure 1B), although the curves here are also similar for times early in the century, as well as from the late 1960's on. As will be shown below, these divergences within r values show up in the form of wide credible sets for certain functions of exposure. Comparing the r=1 and r=2 models, the profiles are roughly similar from the late 60's on, except that the r=1 curves show a more gradual decline than the r=2 curves.

Table 5 gives expected values and 95% credible sets for the functions of exposure described in Section II. D above. Comparing the results for the r=1 and r=2 models, it is seen that the former predicts considerably greater exposure for the decades before 1960 and predicts 15-20% less exposure for e(60s) and e(peak10); for the 1970's and 1980's the estimates are quite comparable.

As suggested by the figures, the width of the (95%) credible sets for functions averaging dose over a decade(s) generally increase as time gets further in the past. Before the 1960's, the credible sets are so wide that we can say little except that the levels were lower than the peak levels. For both r=1 and r=2, the 95% credible set is less than a two-fold range for e(60s) and e(peak10), less than 0.06 for e(80s) and less than 7 years for peak year; further, these credible sets are largely overlapping for the two different r values. Taking the union of the credible sets for r=1 and r=2 results in a combined 95% credible set of (1.2,2.3) pg/kg-day for both e(peak10) and e(60s), a combined credible set of (1962,1971) for peak year and a combined set of (0.03-0.10) pg/kg-day for e(80s). These exposure estimates produced by the r=1 and r=2 models can be compared to the optimal estimate under the constant exposure assumption (i.e., the e(t,Const) model) of 0.38 pg/kg-day.

Figure 2 A,B show surfaces of predicted mean TCDD concentrations in males by birth year and specimen year derived using the two optimal exposure curves (the curves labeled “A” in Figures 1A and 2B, respectively.). Both figures clearly show that, for all birth cohorts, individual concentrations have been declining since 1970. For a given year in the late 80's however, another trend is also evident in both figures; namely, that concentrations tend to increase with age, except in the very young age range where the impact of breast milk exposure is evident. For 1986 the figures show about 3-fold increases from age 20 to age 40 and about 1.3 fold increases from age 40 to age 60. In earlier years, a different age trend may hold, however. For 1974, the surface in figure 2B actually shows slight decreases in concentrations as age increases from 20 to 40 to 60.

It is interesting to contrast these trends to what would likely be observed if past exposure were constant over a long interval. Since the elimination rate k is a decreasing function of body fat and since older persons tend to have higher percentages of body fat, elimination rates tend to decrease with age (equivalently, TCDD has longer half-lives in older persons). Assuming constant past exposure, the PK model predicts that average concentrations in males would increase 16% from age 20 to age 40 and 10% from age 40 to age 60; for females the increases

would be 26% from age 20 to age 40 and 31% from age 40 to age 60.

A final point of interest relates to the impact of breast feeding. As mentioned above, breast feeding only had an impact in the under 15 age groups, where the mean concentrations were 4.2 pg /ml (NHATS 87) and 2.0 pg/ml (NHATS 82). For the under 15 age group in 1982, the expected mean concentrations (using the r=2 model) were 3.8 pg/g in breast fed children versus 0.3 pg/g in non breast-fed children; in 1987 the expected means in this age group were 1.8 pg/g for breast-fed and 0.2 pg/g for non breast-fed. Taking into account a 50% breast-feeding rate, this yields averages of 2.0 pg/g and 1.0 pg/g, for the 82 and 87 NHATS, respectively. The removal of the breast feeding component from the model increased the CHI_{GOF} statistic (i.e., worsened the fit) from 148 to 171; since this component involved no extra fitted parameters, this is evidence that breast-feeding exposure plays an important role in determining body burdens in children.

C. Sensitivity Analysis on Prior

We evaluated the impact of changes in the prior on the expected values of the exposure functions. Specifically, we considered the following alterations in the plausibility criteria: 1) decreasing the maximum ratio of peak to 1900 exposure dose from 200 to 100; 2) decreasing the maximum 1900 exposure dose from 0.5 to 0.25; and 3) decreasing the maximum ratio of peak to 1990 exposure dose from 100 to 50. The results are summarized in Table 6.

It is instructive to compare the magnitude of the change in expected values to the width of the 95% credible set under the original prior; these "relative" changes compare in a rough way the uncertainty across priors to the uncertainty within a prior. In general, the changes tended to be small. The greatest relative change was under alternate prior 3 with r=2 where E(50s) had a relative increase of 0.41.

D. Sensitivity Analysis on PK Parameters

The PK model is the link between current concentrations and past exposure; thus inferences about past exposure depend critically on the PK model. Because the PK model parameters k_0 and k_1 are not definitively known, the sensitivity of the exposure estimates to changes in k_0 and k_1 is of interest (recall that the elimination rate $k = k_0 + k_1 (F(t) - 25) = 0.077 - .00313 (F(t) - 25)$ where F is % body fat). To assess sensitivity, the above analyses with the r=2 model (and the original prior) were reperformed using both the upper and the lower 95% confidence limits on k_0 (with k_1 fixed as above) and on k_1 (with k_0 fixed). Based on our re-analysis of the Michalek et al. (1996) data, the standard errors of the k_0 and k_1 estimates were 0.0057 and 0.00080, respectively. Table 7 shows the changes and relative changes in expected values of the functions of exposures for these alternate values of k_0 and k_1. Here the relative change (absolute change over the width of the 95% credible set derived with the original k_0 and k_1) compares the effects of uncertainty within the PK model to the uncertainty within the prior. Using the lower 95% confidence limit for k_1 resulted in relative increases of greater than 0.65 in e(40s) and e(50s), while using the upper limit for k_1 resulted in a relative decrease of 0.33 in e(60s). Increasing k_0 (to the upper 95% limit) resulted in relative increases of 0.44 in e(60s) and 0.53 in e(peak10). These were the only relative changes greater than 0.3 in absolute value. Note that increasing k_0 increased all the exposure estimates while increasing k_1 increased the estimates

for some decades and decreased estimates for others.

In the constant exposure model, using the upper and lower confidence limits for k_0 resulted in about a +/- 12% change in the optimal fitting dose; with constant dose, the area under the time-by-exposure dose curve (AUC) would change by the same amount. In contrast, with the r=2 model, the expected AUC decreased by 22% using the lower limit and increased by 25% using the upper limit for k_0.

DISCUSSION

We have attempted here to develop and test a methodology for using recent body burden data to predict historical exposure to 2,3,7,8-TCDD. The methodology requires selecting or developing a parameterized pharmacokinetic model relating past exposure to body burden, information on population physiological parameters to substitute into the pharmacokinetic model, and adequate human concentration data. This human data should be characterized by a broad range of both age and specimen year. In addition, a critical part of the methodology is the choice of the parameterization of exposure and the creation of plausibility limits, or more generally, a prior distribution on these parameters. Although these two notions, parameterization and the prior on the parameters, may appear independent, in reality they are linked and both taken together constitute the process of creating a prior distribution on exposure.

The results of this analysis show the necessity of using a Bayesian approach, since, as was apparent in Figures 1A&B, various different parameter values, each representing quite distinct exposure curves, all give approximately the same optimal likelihood values. This fact points up the limits of exposure dose reconstruction; the further back in time from the earliest concentration data, the less the impact on observed concentrations and hence, the less the accuracy in predicting the exposure level. To see this more clearly, suppose that the curve labeled A in Figure 1A represented true exposure from the year X onward and suppose that before the year X exposure were constant. We consider the effect of changes in exposure e(t) before the year X on mean TCDD levels in 1985 in males in the 60-69 age group. If X is the year 1960, then increasing the pre 1960 level from 0.0 to 0.5 pg/kg-day increases the mean from 6.40 to 7.31 pg/g. If X is 1950 then a similar increase (from 0.0 to 0.5) in the pre 1950 level increases the mean from 7.07 to 7.38 pg/g while if X is 1940 a similar increase (from 0.0 to 0.5 in the pre 1940 level) increases the mean only from 7.12 to 7.20 pg/g. Examining the range of the SEM's from Table 1 gives some perspective on what kinds of changes will be detectable; if the increase in the mean is well less than the SEM (as is the case when X=1940) then detecting such differences in past levels will be difficult.

These limitations of exposure reconstruction were reflected in the 95% credible sets which were considerably wider (relative to the mean value) for exposure estimates from earlier as opposed to more recent time periods. For more recent time periods, the credible intervals were relatively narrow and carry useful information about exposure. In addition the sensitivity to changes in the prior (including changes in the r value) was relatively small.

Sensitivity analysis did show that the PK parameters could be quite important in determining the past exposure levels. Changes in these parameters within the limits of uncertainty (i.e., within the 95% confidence interval) could lead to relatively large changes in the past exposure estimates for certain decades. Still, considering the upper and lower limits for both PK

parameters (k_0 and k_1), the expected value of e(peak10) was between 1.6 and 2.3 pg/kg-day, the expected value of e(80s) was between 0.037 and 0.056 pg/kg-day and the expected value of peak year was between 1967 and 1969 (for the r=2 model).

As discussed in the previous section, the observed human concentration data appear inconsistent across and within some of the studies, particularly the 1982 and 1987 NHATS. Currently there is no explanation for the seeming discrepancies in the NHATS results; examination of these two studies showed that the analytical methods with regards to 2,3,7,8-TCDD levels were comparable (Orban et al., 1994). These apparent inconsistencies however may help explain why none of the exposure models considered here, even the very high dimensional parameterization, adequately fit the group mean data. There are probably additional sources of variance across studies and across age groups within studies that are not accounted for by the reported SEM's and which, if considered, could lower the chi-square statistic to within acceptable limits. Interestingly, if one were to combine the 1982 and 1987 NHATS data, taking the weighted average of the age group means, then the resulting age trend would seem reasonable, unlike the age trends within each of the studies. As a further sensitivity analysis, we re-performed our r=2 analysis substituting this combined NHATS data set for the NHATS82 and 87 data sets. This reduced CHI_{GOF} from 148 to 90 (with 3 fewer degrees of freedom) but did not appreciably change the expected values of any of the exposure functions.

It is thought that levels derived from sediment cores should somewhat closely mirror deposition of dioxins from the atmosphere. It is also reasonable to assume that the timing of deposition of dioxins corresponds reasonably closely to the timing of the impact to the food chain and to human exposure. The fact that the peak human exposure year calculated here is quite close to the peak years of deposition (as inferred from lake sediments) reinforces this point. The exposure dose of humans, however, takes into account more factors than just the dioxin dose deposited from the atmosphere. Other factors which affect relative levels of exposure through time include the amount of various food groups (e.g., beef, dairy) eaten, the amount of lean versus fat of various foods eaten, and various possible changes in grazing and slaughtering processes of farm animals. Changes in exposure due to these effects must also be considered when considering the plausibility of the exposure curves generated here.

The estimates derived here suggest that TCDD exposures may have been 20 times higher during the 1960's than during the 1980's. Over a 10 year peak period in the 1960's and early 1970's, daily exposures were estimated to average around 1.5 to 2.0 pg/kg. In contrast, during the 1980's, daily exposures were estimated to average less than 0.10 pg/kg.

In addition to providing broad estimates of past TCDD exposure and providing insight into the relationship between past TCDD exposure and recent body burdens, it is hoped that the general methodology outlined here could be applied by to other long half-life chemicals (including other dioxins and dioxin-like PCB's) or more generally, to other conceptually similar problems.

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Table 1. Mean Human Lipid TCDD Concentrations Reported in Various U.S. Studies.

Study (Reference)	Age/Sex Group	Specimen Year	Sample Size	TCDD Mean, pg/g	Standard Error of the Mean
NHATS 82 (EPA, 91)	0-14, Both	1982	178	4.2	0.69
	15-44, Both	1982	312	6.9	0.87
	45+ , Both	1982	273	5.5	0.84
NHATS 87 (EPA, 91)	0-14, Both	1987	146	2.0	0.82
	15-44, Both	1987	318	4.4	0.52
	45+, Both	1987	401	9.4	0.41
VA/EPA (VA/EPA,1988)	20-36, Male	1971-73	27	19.8	1.2
	23-39, Male	1974-76	29	17.3	1.2
	26-42, Male	1977-79	57	11.6	1.2
	29-45, Male	1980-82	82	12.6	1.2
Andrews et al. (1989)	18-29, Both	1986	14	4.0	0.95
	30-39, Both	1986	30	5.9	0.65
	40-49, Both	1986	25	5.5	0.71
	50-59, Both	1986	22	8.0	0.76
	60-79, Both	1986	37	9.5	0.59
Air Force (Michalek et al., 1997)	35-39, Male	1987	168	3.8	0.23
	40-44, Male	1987	280	4.0	0.18
	45-49, Male	1987	165	4.6	0.23
	50-54, Male	1987	232	4.7	0.20
	55-59, Male	1987	142	4.8	0.25
	60-64, Male	1987	33	5.0	0.52
	65-69, Male	1987	35	6.2	0.51

Table 2. Time Trends for 2378-TCDD.

Reference	Source/Location	Ratio of Peak to Early Century Avg Levels	Ratio of Peak to 1980's Avg Levels	Peak Year
Cleverly et al., 1996	Sediment Cores - 10 U.S. Lakes	19[a]	2.0[b]	1970
Kjeller et al., 1995	Sediment Core in Baltic Proper	16	1.2	1978
Beurskens et al., 1993	Lake in Nether-lands	> 33[c]	20	1965
Kjeller et al., 1991	Herbage Samples, U.K.	2.3	1.4	1960-1970
Huestis et al., 1997	Lake Trout, Lake Ontario	-	> 2.1[d]	<1977[d]

a) For 5 lakes with pre 1920's levels
b) For 2 lakes with 1980's levels
c) Peak was 33 times limit of detection; levels in early 1940's (earliest data) were below limit of detection.
d.) 1977 was the first year with data available

Table 3. Goodness of Fit of Exposure Models

Model	# Parameters	AIC	CHI_{GOF}
$e(t,\theta,.5)$	5	290	280
$e(t,\theta,1)$	5	169	159
$e(t,\theta,2)$	5	158	148
e(t,CONST)	1	366	364
$e(t,\phi)$	38	183	107

Note: 99th percentile chi-square value is 40.3.

Table 4. Predicted versus Observed Mean TCDD Concentrations.

Study	Age/Sex Group	Specimen Year	Observed TCDD Mean, pg/g	Predicted Mean (z-score) r=1	Predicted Mean (z-score) r=2
NHATS 82	0-14, Both	1982	4.2	2.4 (-2.6)	2.0 (-3.1)
	15-44, Both	1982	6.9	5.3 (-1.9)	5.2 (-2.0)
	45+ , Both	1982	5.5	9.0 (4.2)	8.6 (3.6)
NHATS 87	0-14, Both	1987	2.0	1.1 (-1.0)	1.0 (-1.2)
	15-44, Both	1987	4.4	3.1 (-2.4)	2.9 (-2.7)
	45+, Both	1987	9.4	7.1 (-5.6)	6.6 (-6.7)
VA/EPA	20-36, Male	1971-73	19.8	14.2 (-2.8)	17.2 (-1.3)
	23-39, Male	1974-76	17.3	11.7 (-2.8)	13.4 (-2.0)
	26-42, Male	1977-79	11.6	9.3 (-1.7)	9.7 (-1.3)
	29-45, Male	1980-82	12.6	7.4 (-4.5)	7.4 (-4.5)
Andrews et al.	18-29, Both	1986	4.0	2.3 (-1.7)	2.1 (-1.9)
	30-39, Both	1986	5.9	4.5 (-2.2)	4.5 (-2.2)
	40-49, Both	1986	5.5	5.8 (0.4)	5.6 (0.1)
	50-59, Both	1986	8.0	6.8 (-1.6)	6.4 (-2.1)
	60-79, Both	1986	9.5	8.3 (-2.1)	7.7 (-3.2)
Air Force	35-39, Male	1987	3.8	3.9 (0.3)	3.8 (0.0)
	40-44, Male	1987	4.0	4.6 (3.1)	4.4 (2.3)
	45-49, Male	1987	4.6	5.0 (1.5)	4.7 (0.6)
	50-54, Male	1987	4.7	5.3 (3.0)	5.0 (1.7)
	55-59, Male	1987	4.8	5.8 (3.7)	5.5 (2.6)
	60-64, Male	1987	5.0	6.0 (1.9)	5.7 (1.3)
	65-69, Male	1987	6.2	6.6 (0.9)	6.2 (0.2)

Table 5. Expected Values and 95% Credible Sets for Functions of Exposure.

	r = 1		r = 2	
Function of Exposure	Expected Value	Credible Set (95%)	Expected Value	Credible Set (95%)
e(10-39)	0.13	0.02-0.36	0.05	0.02-0.08
e(40s)	0.30	0.10-0.73	0.06	0.03-0.15
e(50s)	0.68	0.46-1.06	0.18	0.04-0.61
e(60s)	1.46	1.21-1.70	1.70	1.26-2.30
e(70s)	0.40	0.32-0.45	0.39	0.10-0.66
e(80s)	0.07	0.06-0.10	0.05	0.03-0.08
e(Peak10)	1.48	1.22-1.81	1.85	1.49-2.32
Peak Year	1965.9	1962.6-1967.9	1968.2	1964.9-1971.0

Note: units are pg/kg-day except for Peak Year.

Table 6. Absolute and Relative Changes in Expected Values under Alternate Priors

Function of Exposure	Alternate Prior 1 [a] ; r=1	Alternate Prior 2 [b]; r=1	Alternate Prior 3 [c]; r=1	Alternate Prior 3 [c]; r=2
e(10-39)	0.06 (0.17)	-0.01 (-0.02)	0.11 (.31)	0.00 (0.05)
e(40s)	0.11 (0.17)	-0.01 (-0.01)	0.20 (.31)	0.03 (0.27)
e(50s)	0.08 (0.14)	-0.01 (-0.01)	0.17 (.29)	0.24 (0.41)
e(60s)	-0.08(-0.16)	0.00 (0.01)	-.13 (-.27)	-0.22 (-.21)
e(70s)	0.00 (0.00)	-0.00 (-0.00)	-0.00(-.03)	0.11 (0.20)
e(80s)	0.00 (0.10)	-0.00 (-0.00)	0.01 (.30)	0.00 (0.04)
e(Peak10)	-0.07 (-.13)	0.00 (0.00)	-0.13 (-.22)	-0.27 (-0.32)
Peak Year	0.4 (0.08)	-0.0 (-0.01)	0.5 (0.09)	1.2(0.19)

Change is expected value under alternate prior minus expected value under original prior. Relative change, in parenthesis, is change over the width of the 95% credible set with original prior, shown in Table 5.

a - Alternate Prior 1 changes plausible range for ratio of peak to 1900 exposure from [2,200] to [2,100].

b - Alternate Prior 2 changes plausible range for 1900 exposure from [0,0.5] to [0,0.25].

c - Alternate Prior 3 changes plausible range for ratio of peak exposure dose to 1990 exposure dose from [1,100] to [1,50].

Note: for r=2 using alternate priors 1 or 2 gave essentially the same expected values as did the original prior; hence these are not shown.

Table 7. Changes and Relative Changes in Expected Values under Alternate k Values.

Function of Exposure	k_0=Lower 95% Limit	k_0 =Upper 95% Limit	k_1=Lower 95% Limit	k_1=Upper 95% Limit
e(10-39)	-.01 (-.23)	0.01 (.15)	-0.01 (-.14)	-0.01(-.11)
e(40s)	-.02 (-.17)	0.01 (.06)	0.09 (.68)	-0.02(-.13)
e(50s)	-0.13 (-.23)	0.05 (.08)	0.54 (.95)	-0.13 (-.23)
e(60s)	-0.26 (-.26)	0.46(.44)	0.10(.09)	-0.34 (-.33)
e(70s)	-0.11 (-.20)	0.09(.09)	-0.06 (-.10)	0.15 (.27)
e(80s)	-0.01 (-.24)	0.01(.16)	-0.01 (-.22)	-0.01 (-.11)
e(Peak10)	-0.24 (-.29)	0.44 (.53)	-0.02(-.03)	-0.06 (-.07)
Peak Year	-0.7 (-.11)	-0.8 (-.14)	0.2 (.03)	0.7 (0.11)

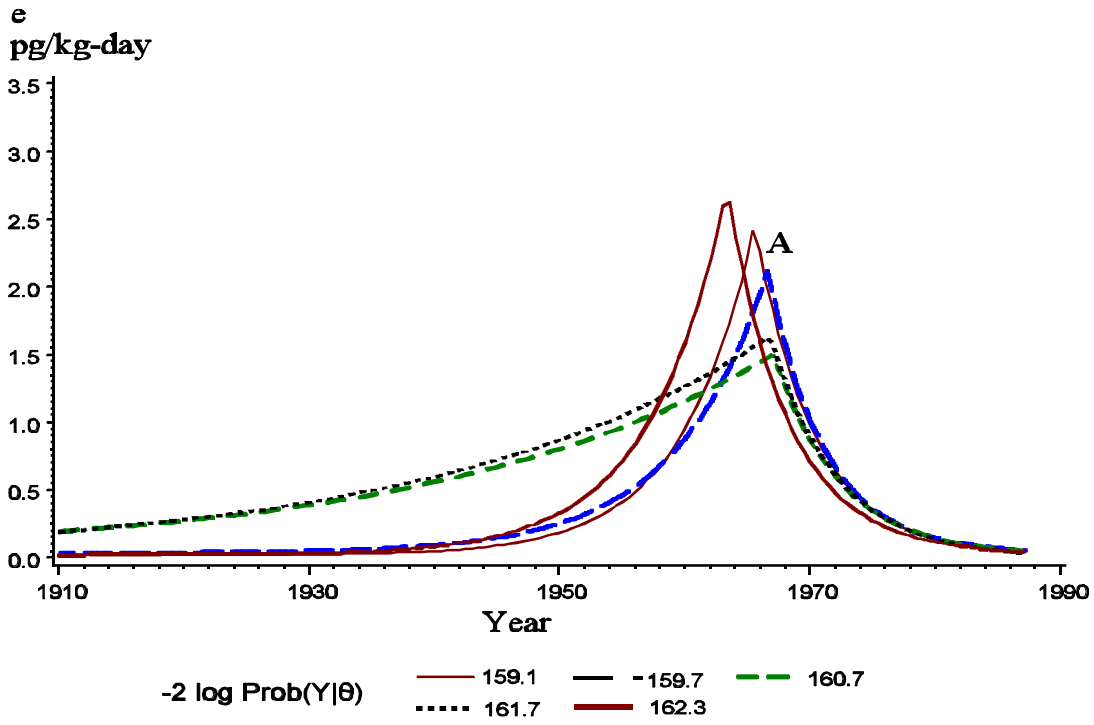
Change is expected value under alternate k_0 or k_1 value minus expected value under original (k_0,k_1). Relative change, in parenthesis, is change over the width of the 95% credible set with original (k_0,k_1), shown in Table 5.

Figures

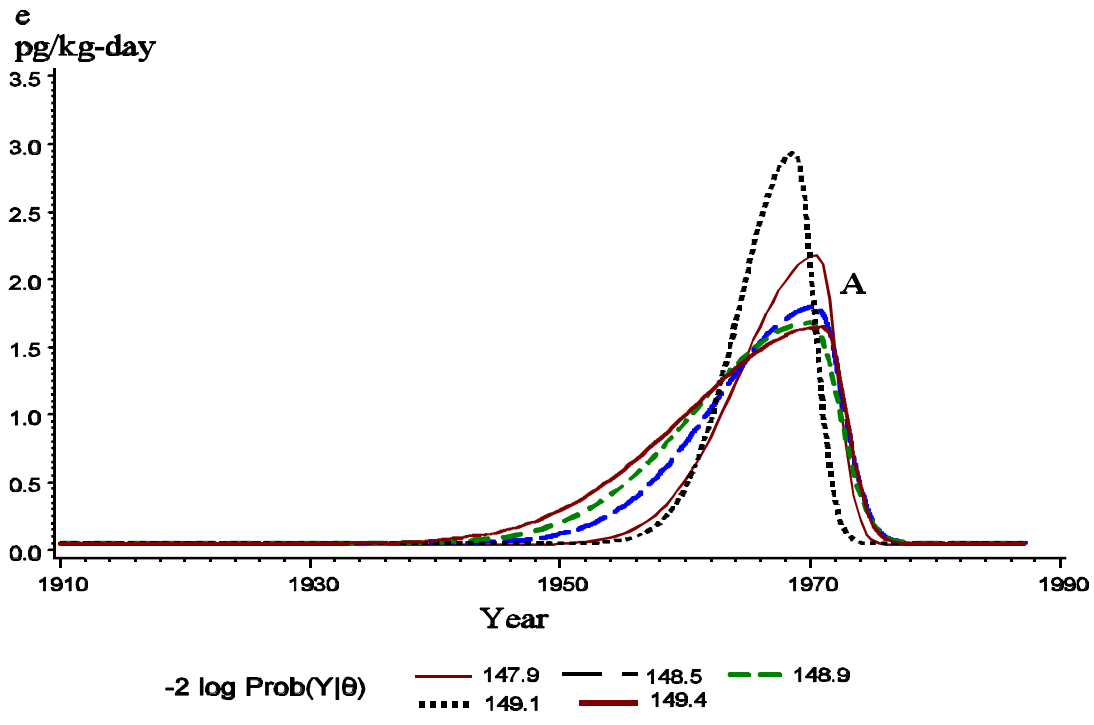
Fig 1A,B. Exposure curves $e(t,\theta, r)$ giving optimal fits to human concentration data with r=1 (Fig 1A) and r=2 (Fig 1B). For each r, a sample of θ values was generated from the prior distribution $\Pi(\theta)$. The five θ values giving the highest value of -2 log $Prob(y|\theta)$ were identified and the corresponding curves $e(t,\theta,r)$ are shown here.

Fig 2A,B. Predicted mean TCDD lipid concentrations (pg/g) in males by birth year and specimen year derived using $e(t ,\theta,r)$ curves shown in Figure 1A,B and PK model. Fig. 2A (2B) was derived using curve labeled "A" in Fig 1A (1B).

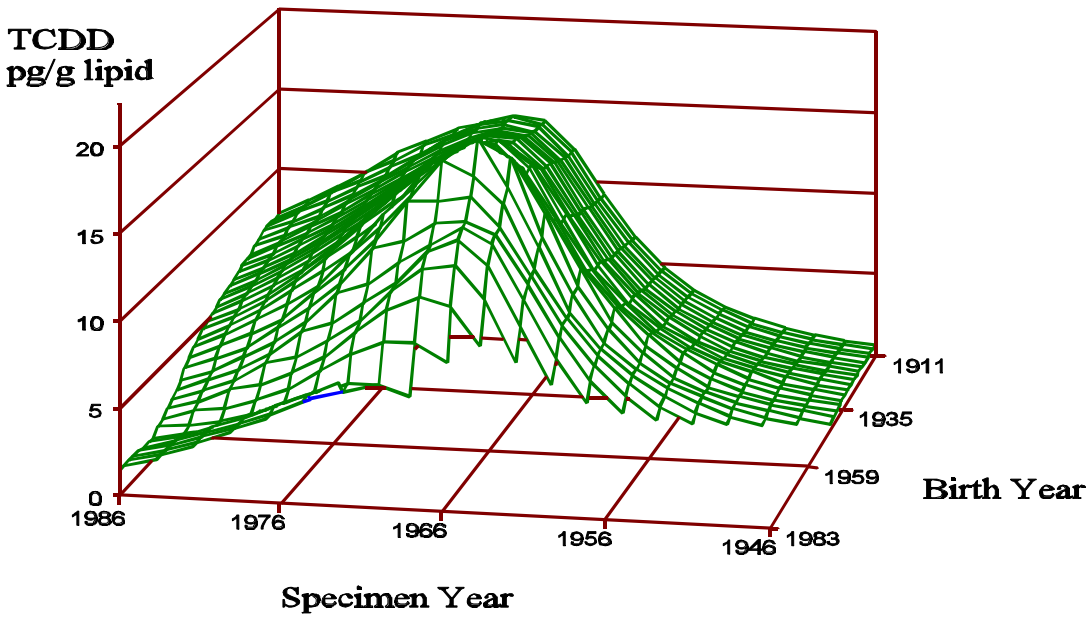
(a)


e
pg/kg-day
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
A
1910
1930
1950
1970
1990
Year
-2 log Prob(Y|θ)
159.1
159.7
160.7
161.7
162.3

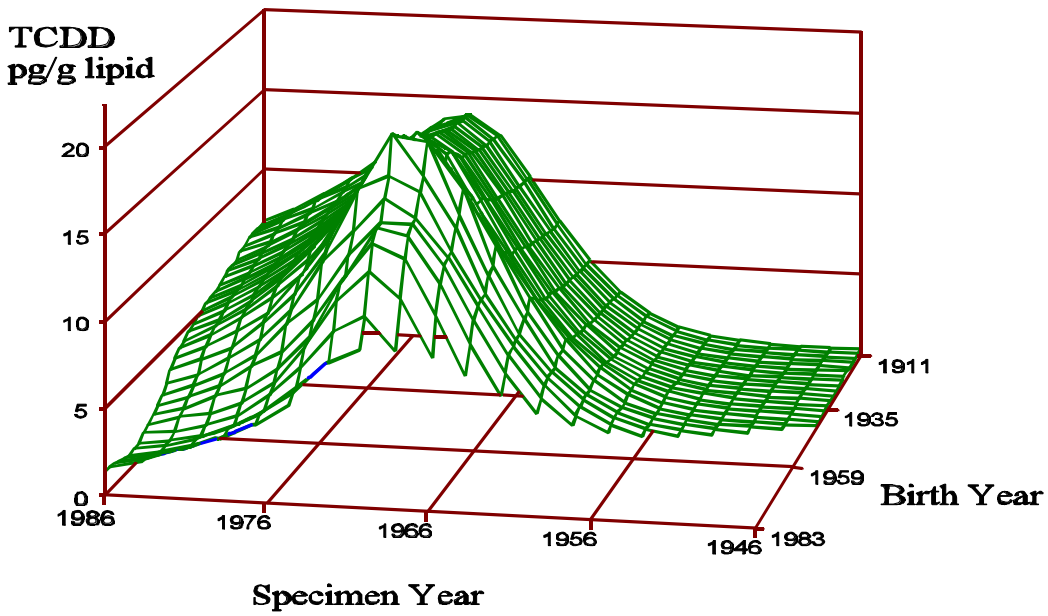
(b)


e
pg/kg-day
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
A
1910
1930
1950
1970
1990
Year
-2 log Prob(Y|θ)
147.9
148.5
148.9
149.1
149.4

(a)


TCDD
pg/g lipid
20
15
10
5
0
1986
1976
1966
1956
1946
1911
1935
1959
1983
Birth Year
Specimen Year

(b)


TCDD
pg/g lipid
20
15
10
5
0
1986
1976
1966
1956
1946
1911
1935
1959
1983
Birth Year
Specimen Year

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